Chapter 2: Multi-Component Synthesis of Tetrahydrobenzo[b]pyrans

**Introduction:**

Chemistry of heterocycles has been of importance in understanding the formation of bioactive molecules as well as having industrial applications especially in pharmaceuticals. The majority of pharmaceuticals and biologically active agrochemicals contain heterocyclic moieties with addition of countless additives and modifiers. The applications ranging from cosmetics, reprography, information storage and plastics heavily depend upon the heterocyclic residues. One of the striking structural features inherent to heterocycles, which is continued to be exploited to a great advantage by the drug industry, lies in their ability to manifest substituent around a core scaffold in well defined three-dimensional representations. Based upon these considerations in recent years, a family of new heterocyclic scaffolds has come into existence having wide range of applications such as switching on / off devices, photo catalysis, etc. Tetrahydrobenzo[b]pyrans [Fig. 1], synthesized in this work are fused six membered heterocyclic compounds which have attracted the attention of both synthetic chemists as well as pharmacists due to plethora of applications possible for their derivatives.

![Structure of tetrahydrobenzo[b]pyran](Fig. 1)

**Applications of Tetrahydrobenzo[b]pyrans:**

Tetrahydrobenzo[b]pyrans have recently attracted attention as an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals due to their wide applications [Fig. 2]. These compounds are widely used as anti-coagulant, diuretic, spasmolytic, anticancer and anti-anaphylactin agents. They can also be used as cognitive
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enhancers for the treatment of neurodegenerative disease as Alzheimer’s disease, amyoprophic lateral sclerosis, Huntington’s disease, Parkinson’s disease, AIDS associated dementia and Down’s syndrome as well as for the treatment of schizophrenia and myoclonus. Other than their biological importance, some 2-amino-4H-pyrans have been widely used as photoactive materials. In addition, the tetrahydrobenzo[b]pyran nucleus is an important structural scaffold of a series of natural products and can be converted into pyridine systems which relate to pharmacologically important calcium antagonists of the dihydropyridine [DHP] types.

Synthetic Methods for Benzopyrans:

i) Tetrahydrobenzo[b]pyrans can be synthesized by two component condensation of arylmethylene malononitrile or arylmethylene cyanoacetate with dimedone. Tu and co-workers synthesized a series of tetrahydrobenzo[b]pyran derivatives by the reaction of cyano-olefin and dimedone in ethylene glycol at 80 °C without catalyst in 61-96 % yield. [Scheme1].
Multi-component reactions (MCRs) have attracted considerable attention since they are performed without need to isolate any intermediate during their processes which reduces time as well as saves energy and raw materials\textsuperscript{10}. These are superior to two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules. Taking into consideration these advantages, an efficient and convenient synthesis of tetrahydrobenzo[b]pyrans can generally be carried out via a one-pot, three component condensation of an aromatic aldehyde, an active methylene compound and dimedone under influence of acidic/basic/bi-functional or phase transfer catalysts\textsuperscript{11} [Scheme 2].

\begin{equation}
\text{ArCHO} + \text{HCN} + \text{HCN} \xrightarrow{\text{Catalyst}} \text{Scheme 2}
\end{equation}

ii) Balalaie \textit{et al.}\textsuperscript{12} have used diammonium hydrogen phosphate to synthesize novel 4H-benzo[b]pyrans \textit{via} one-pot, three-component tandem Knoevenagel cyclocondensation reaction, consisting of aromatic aldehyde, malononitrile and barbituric/thiobarbituric acid in aqueous ethanol at room temperature [Scheme 3].

\begin{equation}
\text{ArCHO} + \text{HCN} + \text{HCN} \xrightarrow{\text{DAHP (10mol\%)} \text{aq. EtOH, r.t.}} \text{Scheme 3}
\end{equation}

iii) Perumal and co-workers\textsuperscript{13} found InCl\textsubscript{3}-ethanol combination useful for the synthesis of new type of benzopyrans \textit{via} phosphorus-carbon bond formation by multi-component reaction of salicylaldehyde, malononitrile with triethyl phosphate in good yields [Scheme 4].
iv) Pyranopyrazoles are the new class of benzopyrans having important biological properties which stimulated interest to develop new methods for their synthesis.

   a) Litvinov et al.\textsuperscript{14a} used triethyl amine as a catalyst for synthesis of 6-aminopyran [2,3-\(c\)]pyrazol-5-carbonitriles by four-component reaction of aromatic aldehydes, malononitrile, \(\beta\)-ketoesters and hydrazine hydrate in good to excellent yields [Scheme 5].

   b) Kumaravel and his group\textsuperscript{14b} synthesized a new pyrazolyl-4\(H\)-chromene derivatives in water at ambient temperature by replacing aldehyde by \(o\)-hydroxybenzaldehyde keeping other reactants same as in Scheme 5 [Scheme 6].

   c) Shestopalov and co-workers\textsuperscript{14c} carried out three-component condensation of 4-piperidinone, 5-pyrazolone and malononitrile by electrochemical means, which yielded 6-amino- 5-cyano- spiro- 4- (piperidine-4\(\epsilon\))- 2\(H\), 4\(H\)-dihydropyrazolo[3,4-\(b\)]pyran [Scheme 7].
They claimed that the electrochemical reactions proceed under milder conditions with the yields 12-15 % greater than those of the reactions catalyzed by chemical bases.

![Scheme 7](image)

**Scheme 7**

d) The first enantioselective synthesis of biologically active 6-amino-5-cyanodihydropyrano[2,3-c]pyrazoles was carried out by Gogoi and co-workers^{14d} by a tandem Michael addition and Thorpe-Ziegler type reaction between 2-pyrazolin-5-ones and benzyldiene malononitriles catalyzed by cinchona alkaloid catalyst [Scheme 8].

![Scheme 8](image)

**Scheme 8**

v) Luo *et al.*^{15} reported asymmetric tandem oxo-Michael-aldol reaction of salicylaldehyde derivatives with \( \alpha,\beta \)-unsaturated aldehydes using a chiral amine/chiral acid organocatalytic system as a catalyst. The organocatalytic system of (S)-diphenylpyrrolinol trimethylsilyl ether with chiral shift reagent (S)-Mosher acid presented a synergistic effect in the improvement of reaction performance and offered an efficient steric effect in the transformation. The tandem oxo-Michael-aldol reaction proceeded with high yields (up to 90%) and excellent enantioselectivities (ee up to 99%) to give the corresponding chromene derivatives [Scheme 9].

![Scheme 9](image)

**Scheme 9**
vi) A combinatorial library of the 2-alkylamino-3-nitro-4-alkylsulfanyl, 4H-chromenes was synthesized by Rao and his group\(^1\) in excellent yields by base-catalyzed reaction of the nitroketene \(N,S\)-acetals and the ring substituted \(o\)-hydroxybenzaldehydes. Nucleophilic displacement of the C-4 alkylsulfanyl group with different thiols afforded 4H-chromenes with structural diversity [Scheme 10].

![Scheme 10](image)

vii) Selvam et al.\(^1\) achieved an efficient synthesis of pyrano[2,3-b]pyridines with the help of SnCl₂·2H₂O (Lewis acid) mediated Friedlander reaction of 2-amino-3-cyano-4H-pyran with cyclopentanone / cyclohexanone under solvent-free condition [Scheme 11].

![Scheme 11](image)

viii) Xanthenes have been used as versatile synthons due to the inherent reactivity of the inbuilt pyran ring. These benzopyran derivatives can be synthesized by the reaction of substituted salicylaldehydes with dimedone / cyclohexane-1,3-dione under influence of acidic catalysts such as KF/ Al₂O₃\(^1\), triethylbenzlammonium chloride (TEBA)\(^1\), TCT\(^2\), Cerium(III) chloride\(^3\), etc. [Scheme 12].

![Scheme 12](image)
ix) Coumarins are the important derivatives of benzopyrans which are generally synthesized by Pechmann\textsuperscript{22} [Scheme 13], Knoevenagel\textsuperscript{23} [Scheme 14], Perkin\textsuperscript{24} [Scheme 15], Reformatsky\textsuperscript{25} [Scheme 16] and Wittig\textsuperscript{26} [Scheme 17] reactions under influence of acidic or basic catalysts.
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Catalysts for Tetrahydrobenzo[b]pyrans:

Tetrahydrobenzo[b]pyrans can be synthesized either using acidic or basic catalysts under different experimental conditions. A detailed literature survey towards the multi-component synthesis of tetrahydrobenzo[b]pyrans revealed that most of the protocols employed for this reaction operate under high thermal activation\(^\text{27}\), microwave activation\(^\text{28}\) and ultrasonic irradiation\(^\text{29}\). Recently, Fotouhi \textit{et al.}\(^\text{30}\) reported electrochemical synthesis of tetrahydrobenzo[b]pyrans. There are few protocols operable at room temperature using \textit{N}-methylimidazole\(^\text{31}\), (S)-proline\(^\text{32}\) and (D,L)-proline\(^\text{33}\). Each of the above method has its own merit with at least one of the limitations of low yields, commercially unavailable catalysts, long reaction times, harsh reaction conditions and tedious work-up procedures. Hence, improved methods for multi-component synthesis of tetrahydrobenzo[b]pyran using inexpensive and less toxic reagents coupled with simple reaction conditions and easier work-up procedures are required.

Our earlier experience on potassium phosphate directed us that it would overcome the above said drawbacks occurred during the synthesis of tetrahydrobenzo[b]pyrans.

Applications of K\(_3\)PO\(_4\) in Our Laboratory:

We have studied alkylations of Meldrum’s acid\(^\text{34}\) [Scheme 18], Henry reaction for synthesis of nitroaldols\(^\text{35}\) [Scheme 19], Claisen-Schmidt condensation for synthesis of chalcones\(^\text{36}\) [Scheme 20] and Michael addition of thiols to \(\alpha,\beta\)-unsaturated ketones\(^\text{37}\)[Scheme 21] using anhydrous K\(_3\)PO\(_4\) as a base. As a continued research towards K\(_3\)PO\(_4\), we explored its efficacy in multi-component synthesis of tetrahydrobenzo[b]pyrans.
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Scheme 18

Alkylation Of Meldrums Acid

Scheme 19

Nitroaldol Condensation

Scheme 20

Synthesis Of Chalcones

Scheme 21

Michael Addition
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Objectives:

Our aim for undertaking this work as outlined above was

i) To find out the ways to overcome the limitations and drawbacks of the reported methods such as harsh reaction conditions, use of expensive catalysts.

ii) To develop a one-pot synthesis of tetrahydrobenzo[b]pyrans at room temperature from aldehyde, malononitrile and dimedone using a commercially available reagent and

iii) To find out the role of catalyst and to depict mechanistic pathway for the formation of tetrahydrobenzo[b]pyrans.

Present Work:

In continuation with our earlier experience with potassium phosphate in Michael addition\textsuperscript{36}, we envisaged that K\textsubscript{3}PO\textsubscript{4} could be a suitable catalyst for the present transformation, as potassium is oxophilic, the central K\textsuperscript{+} will make a strong co-ordinate bond with ‘O’ of 1,3-diketone to form its enolate ion (6). The counteranion PO\textsubscript{4}\textsuperscript{3−} is sufficiently basic for the formation of cyanoolefin (5) and subsequent Michael addition of enolate of 1,3-diketone (6) on cyanoolefin (5), followed by cyclocondensation to form corresponding tetrahydrobenzo[b]pyran (4). To remove the conflict that amongst two active methylene compounds viz dimedone and malononitrile which competitively undergo Knoevenagel condensation with aldehyde, we have carried out reaction of dimedone and aldehyde (1:1) in ethanol using K\textsubscript{3}PO\textsubscript{4} at room temperature for an hour. However, we could obtain only reactants. Based on this a plausible mechanism for the multi-component synthesis of tetrahydrobenzo[b]pyran using K\textsubscript{3}PO\textsubscript{4} in ethanol is suggested [Scheme 22].
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Scheme 22: A plausible mechanism for formation of tetrahydrobenzo[b]pyran

Initially, the reaction of anisaldehyde (1), dimedone (2), malononitrile (3) and potassium phosphate was carried out in ethanol medium at room temperature [Scheme 23]. The corresponding 2-amino-3-cyano-7,7-dimethyl-5-oxo-4-(4-methoxy phenyl)-5,6,7,8-tetrahydro-4H-benzo[b]pyran was obtained in excellent yield within short reaction time. Encouraged by this result, we then employed this reaction as a template to optimize the reaction conditions.

Scheme 23: Potassium phosphate catalyzed multi-component synthesis of tetrahydrobenzo[b]pyrans
A brief screening of solvents showed that water, chloroform, methanol, acetonitrile and ethanol were less effective than mixed solvent system H₂O : C₂H₅OH (80:20, v/v). We also found that the reaction carried out with other potassium sources such as KH₂PO₄, K₂HPO₄, K₂CO₃ also gave inferior results. It is known that aqueous ethanol solutions below 10 % concentration are characterized by hydrophobic hydration. Many Sₜ¹ reactions as hydrolysis of t-BuCl exhibit extrema in thermodynamic as well as in kinetic rate studies. Probably such mixtures stabilize the transition state involving aductation. Upon examining the influence of the amount of anhydrous K₃PO₄ on the reaction, it was found that 15 mol % of anhydrous K₃PO₄ was sufficient to promote the reaction. In the presence of less than this amount, the yield dropped dramatically, even if reaction performed for longer time (Table 1, entry 9). When the amount of anhydrous K₃PO₄ was increased over 15 mol %, neither the yield nor the reaction time was found to be improved (Table 1, entry 10).

Table 1: Optimization of reaction conditions for the synthesis of Tetrahydro benzo [b]pyrans

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent*</th>
<th>Catalyst</th>
<th>Mol %</th>
<th>Time (min)</th>
<th>Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>K₃PO₄</td>
<td>15</td>
<td>120</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>K₃PO₄</td>
<td>15</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN</td>
<td>K₃PO₄</td>
<td>15</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>CH₃OH</td>
<td>K₃PO₄</td>
<td>15</td>
<td>65</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>C₂H₅OH</td>
<td>K₃PO₄</td>
<td>15</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>H₂O + C₂H₅OH(90:10)</td>
<td>K₃PO₄</td>
<td>15</td>
<td>75</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>K₃PO₄</td>
<td>15</td>
<td>50</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>H₂O + C₂H₅OH(70:30)</td>
<td>K₃PO₄</td>
<td>15</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>9</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>K₃PO₄</td>
<td>10</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>K₃PO₄</td>
<td>20</td>
<td>45</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>K₂CO₃</td>
<td>15</td>
<td>75</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>KH₂PO₄</td>
<td>15</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>H₂O + C₂H₅OH(80:20)</td>
<td>K₃HPO₄</td>
<td>15</td>
<td>80</td>
<td>81</td>
</tr>
</tbody>
</table>

* Reaction conditions: anisaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), H₂O: ethanol [80:20, 5 mL], room temp;
* yields refer to pure isolated products;
* Entries in bracket indicate the ratio of H₂O to C₂H₅OH on volume.
To check the generality of the present protocol under the optimized reaction conditions, the reaction was then extended for a variety of aldehydes bearing electron donating substituent in H$_2$O : C$_2$H$_5$OH (80:20, v/v) as a medium using K$_3$PO$_4$ as a catalyst at ambient temperature to yield different substituted tetrahydrobenzo[b]pyrans. The reactions proceeded efficiently in all the cases yielding products in acceptable yields and having high purity. The results are summarized in (Table 2). The structures of the prepared compounds were established unambiguously using spectral methods.

IR spectrum (Fig. 3) of the product (entry 4c, table 2) obtained by reaction of 4-isopropylbenzaldehyde, dimedone and malononitrile showed the absence of carbonyl from aldehyde. In IR spectrum stretching frequency of the starting carbonyl group disappeared from the given 1710-1720 cm$^{-1}$ and appeared at 1656 cm$^{-1}$ because of formation of $\alpha$, $\beta$-unsaturated carbonyl compound. The $^1$H NMR spectrum (Fig. 4) of the same compound showed a two different singlet at $\delta$ 1.05 and 1.11 for three protons each of two methyl groups from dimedone moiety, another set of singlet was observed at 1.19, 1.21 due to three protons of two methyl groups from isopropyl moiety, methylene protons of dimedone moiety appeared as singlet at 2.22 ‘$a$’ to carbonyl group, while other methylene protons of same moiety appeared as singlet at 2.45, other signals appeared as a multiplet at 2.83 for methine proton of isopropyl group, a singlet at 4.37 due to benzylic methine proton, singlet at 4.52 due to –NH$_2$. The aromatic region appeared as singlet at 7.12. CMR (Fig. 5) spectrum of the same compound shows signal at 23.86, 27.75, 28.79, 29.64, 32.16, 33.63, 35.02, 40.66, 50.67, 63.59, 114.15, 118.81, 126.60, 127.29, signals at 140.50 and 147.42 due to olefinic carbons attached to –CN and –NH$_2$ group, respectively while other olefinic carbons at 157.50, 161.46 and at 195.93 due to carbonyl carbon. IR, NMR data is in agreement with the expected structures.

The IR spectrum (Fig. 6) of 2-amino-4-(2,5-dimethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4d, table 2) obtained by multi-component reaction of 2,5-dimethylbenzaldehyde, dimedone and malononitrile showed the expected bands at 3409 and 3318 cm$^{-1}$ due to primary amine, 2191 cm$^{-1}$ due to nitrile group and at 1659 cm$^{-1}$ due to $\alpha$, $\beta$-unsaturated carbonyl group. $^1$H-NMR of 4d (Fig. 7) also supported the structure of the compound and exhibited peaks at $\delta$ 1.06, 1.11 as two singlets corresponding to two methyl groups of dimedone, methylene protons of
dimedone appeared at 2.20, 2.47 as singlets, methyl group protons attached to aromatic ring appeared at 2.22, 2.52 as singlets. Two singlets were observed at δ 4.49, 4.63 for protons of primary amine group and benzylic methine proton, respectively. Aromatic protons appeared at 6.73 as singlet for one proton, 6.87 as doublet for one proton and 7.0 as doublet for one proton. CMR (Fig. 8) spectrum of the same compound shows signals at 19.07, 21.13, 27.58, 28.95, 30.95, 32.29, 40.63, 50.60, 114.67, 127.75, 128.04, 130.41, 132.65, 135.56, 141.66, 157.13, 161.56, 161.56 and carbonyl carbon signal at 195.95.

The IR spectrum (Fig. 9) of 2-amino-4-cyclohexyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4 i, table 2) showed two prominent bands at 3414 and 3249 cm⁻¹ corresponding to primary amine and –CN appeared at 2193 cm⁻¹. Band at 1654 cm⁻¹ marked the presence of α, β-unsaturated carbonyl group. The ¹H–NMR spectrum of the compound 4 i (Fig. 10) has two singlets at δ 1.11, 1.16 for protons of two methyl groups of dimedone and a multiplet of eleven protons of cyclohexyl group observed at δ 1.24-1.71. Four protons of the two methylene groups of dimedone moiety appeared at 2.28 and 2.37 ppm. Benzylic methine proton and primary amine protons showed doublet at 3.30 and a singlet at 4.53, respectively. ¹³C-NMR spectrum (Fig. 11) of the same compound showed peaks at δ 26.19, 26.31, 26.56, 27.41, 27.84, 29.27, 30.52, 32.05, 34.74, 40.67, 43.79, 50.84, 58.91, 114.18, 120.23, 159.87, 163.12, 196.46 corresponding to 18 carbons of the 4 i molecule. Peak at 196.46 is the indication of carbonyl carbon.

We then diverted our attention towards aldehydes bearing electron withdrawing substituents viz –Cl, -NO₂, -CN and found that there is no noticeable effect of substituent on the rate of reaction.

To check efficacy of potassium phosphate, we decided to replace dimedone by cyclohexane-1,3-dione. We observed that present protocol works equally well with dimedone as well as with cyclohexane-1,3-dione.

IR spectrum (Fig. 12) of compound 2-amino-4-(4-cyanophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4 m, table 2) showed bands at 3423, 3334 cm⁻¹ indicating the presence of primary amine group in moiety. Presence of nitrile group is confirmed by prominent peak at 2199 cm⁻¹. α, β-unsaturated carbonyl group from the structure appeared at 1653 cm⁻¹. ¹H-NMR (Fig. 13) of the same compound executed three
multiplets at up-field region of the spectra having values $\delta$ 1.94-2.13, 2.35-2.39, and 2.58-2.64 corresponding to three methylene group protons of cyclohexane-1,3-dione ring moiety. Benzylic methine proton appeared as singlet at 4.47 while protons from primary amine group also exhibited singlet at 4.66 ppm. Four aromatic protons from 4-cyanophenyl ring appeared in characteristic “doublet of the doublet” (dd) manner with 7.37 and 7.59 ($J = 8$ Hz). $^{13}$C-NMR spectra (Fig. 14) of 4 m furnished carbon signals at 20.09, 27.04, 35.73, 36.61, 100, 110, 114.31, 118.81, 128.82, 132.64, 148.61, 158, 163.89 and 195.84.

After a careful literature survey, it is essential to state that, synthesis of tetrahydrobenzo[b]pyrans involving organometallic moiety remained ignored and hence we have focussed our attention towards ferrocene carboxyaldehyde. Gratifyingly, we achieved tetrahydrobenzo[b]pyran of ferrocene carboxyaldehyde in good yield. [Scheme 24] (entry 4n, Table 2).

**Scheme 24**: Potassium phosphate catalyzed synthesis of tetrahydrobenzo[b]pyran of ferrocene carboxyaldehyde

The IR spectrum (Fig. 15) of 2-amino-4-(2,5-dimethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4n, table 2) obtained by multi-component reaction of ferrocene carboxyaldehyde, dimedone and malononitrile showed the expected bands at 3378 cm$^{-1}$ due to primary amine, 2185 cm$^{-1}$ due to nitrile group and at 1645 cm$^{-1}$ due to $\alpha,\beta$-unsaturated carbonyl group. $^1$H-NMR of 4n (Fig. 16) also supported the structure of the compound and exhibited peaks at $\delta$ 0.96, 1.08 as two singlets corresponding to protons of two methyl groups of dimedone, protons of two methylene groups of dimedone appeared at 2.26 and 2.32 as singlets. The protons of ferrocene ring appeared in the region of 3.87-4.22 ppm. Two singlets were observed at 4.36, 4.68 for the protons of benzylic methine proton and primary amine group, respectively. CMR (Fig. 17) spectrum of the same compound shows signals at $\delta$ 27.21,
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28.45, 29.03, 32.13, 40.61, 50.76, 61.11, 65.73, 66.70, 66.99, 68.09, 69.14, 93.41, 100.00, 160.07, 161.46, and carbonyl carbon signal at 196.18.

**Table 2: Potassium phosphate catalyzed multi-component synthesis of tetrahydrobenzo[b]pyrans at room temperature**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product (4)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>MP Obs.(lit.°C)</th>
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<tr>
<td>a</td>
<td><img src="image" alt="Structure a" /></td>
<td>45</td>
<td>94</td>
<td>228-230 (228-230)</td>
</tr>
<tr>
<td>b</td>
<td><img src="image" alt="Structure b" /></td>
<td>50</td>
<td>94</td>
<td>200 (201)</td>
</tr>
<tr>
<td>c</td>
<td><img src="image" alt="Structure c" /></td>
<td>50</td>
<td>91</td>
<td>198-200</td>
</tr>
<tr>
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<td><img src="image" alt="Structure d" /></td>
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<td>240-242</td>
</tr>
<tr>
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<td><img src="image" alt="Structure e" /></td>
<td>60</td>
<td>93</td>
<td>211-212 (209-211)</td>
</tr>
<tr>
<td>f</td>
<td><img src="image" alt="Structure f" /></td>
<td>45</td>
<td>89</td>
<td>212-214 (212-214)</td>
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<tr>
<td>g</td>
<td><img src="image" alt="Structure g" /></td>
<td>60</td>
<td>91</td>
<td>224-226 (227-230)</td>
</tr>
</tbody>
</table>
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a All products showed satisfactory spectroscopic data. (IR, 1H and 13C NMR, MS).
b Yields refer to pure, isolated products.
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Conclusion:

We are successful in developing efficient method for multi-component synthesis of tetrahydrobenzo[b]pyran at ambient temperature using anhydrous K$_3$PO$_4$ as an inexpensive catalyst. This procedure offers several advantages including mild condition, high yields, inexpensive catalyst, wide scope of substrates and operational simplicity, simple work-up, and purification of products by non-chromatographic methods, i.e. by simple recrystallization from ethanol.

Experimental:

Various aldehydes (Lancaster and Alfa-Aesar), 1,3-diketones viz cyclohexane-1,3-dione (Alfa-Aesar) and dimedone(Thomas Baker) were used as received.

IR spectra were recorded on Perkin-Elmer [FT-IR-783] spectrophotometer. NMR spectra were recorded on Bruker AC or MSL (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) spectrometer in CDCl$_3$ using TMS as an internal standard and $\delta$ values are expressed in ppm. Melting points recorded are uncorrected.

Typical Procedure:

A mixture of aldehyde (1 mmol), malononitrile (1 mmol), 1,3-diketone (1 mmol) and K$_3$PO$_4$ (21 mg, 15 mol %) in 20 % ethanol (5 mL) was stirred at r.t. for the time indicated in Table 2. The reaction mixture was poured into ice water and just filtered to yield corresponding tetrahydrobenzo[b]pyran. The residue was purified by recrystallization in ethanol to provide the desired product.
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Spectroscopic Data:

2-amino-4-(4-isopropylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4c, table 2):

\[
\text{Mp.} 198-200 \, ^{\circ} \text{C IR (KBr): 3369, 3181, 2984, 2185, 1656, 1509, 1469, 1408, 1363, 1249, 778, 696 \, \text{cm}^{-1}; \, ^{1}H \, \text{NMR (300 MHz, CDC}_{13}\text{): 1.05 (s, 3H, CH}_{3}\text{), 1.11 (s, 3H, CH}_{3}, 1.19 (s, 3H, CH}_{3}, 1.21 (s, 3H, CH}_{3}\text{), 2.22 (s, 2H, -CH}_{2}\text{), 2.45 (s, 2H, -CH}_{2}\text{), 2.83 (m, 1H, CH}_{3}\text{-CH-CH}_{3}\text{), 4.37 (s, 1H), 4.52 (s, 2H, NH}_{2}\text{), 7.12(s, 4H, Ar-H); \, ^{13}C \, \text{NMR (75 MHz, CDCl}_{3}\text{): \delta 23.86, 27.75, 28.79, 29.64, 32.16, 33.63, 35.02, 40.66, 50.67, 63.59, 114.15, 118.81, 126.60, 127.29, 140.50, 147.42, 157.50, 161.46, 195.93.}
\]

2-amino-4-(2,5-dimethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4d, table 2):

\[
\text{Mp.} 240-242 \, ^{\circ} \text{C IR (KBr): 3409, 3315, 3045, 2963, 2927, 2191, 1659, 1692, 1500, 1461, 1404, 1367, 814, 769 \, \text{cm}^{-1}; \, ^{1}H \, \text{NMR (300 MHz, CDC}_{13}\text{): 1.06 (s, 3H, CH}_{3}\text{), 1.11 (s, 3H, CH}_{3}, 2.21 (s, 2H, -CH}_{2}\text{), 2.22 (s, 2H, CH}_{3}\text{), 2.47 (s, 2H, -CH}_{2}\text{), 2.52 (s, 3H, -CH}_{3}\text{), 4.49 (s, 2H, NH}_{2}\text{), 4.63 (s, 1H, -CH), 6.73(s, 1H, Ar-H), 6.87(d, J = 8 Hz,1H, Ar-H), 7.0(d, J = 8 Hz,1H, Ar-H); \, ^{13}C \, \text{NMR (75 MHz, CDCl}_{3}\text{): \delta 19.07, 21.13, 27.58, 28.95, 30.95, 32.29, 40.63, 50.60, 114.67, 127.75, 128.04, 130.41, 132.65, 135.56, 141.66, 157.13, 161.56, 195.95.}
\]

2-amino-4-cyclohexyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (entry 4i, table 2):

\[
\text{Mp.} 209-210 \, ^{\circ} \text{C IR (KBr): 3414, 3327, 3249, 2923, 2193, 1675, 1654, 1594, 1380, 1251, 693 \, \text{cm}^{-1}; \, ^{1}H \, \text{NMR (300 MHz, CDC}_{13}\text{): \delta 1.11 (s, 3H,CH}_{3}\text{), 1.16 (s, 3H, CH}_{3}, 1.24-1.71 (m, 11H), 2.9 (s, 2H, -CH}_{2}\text{), 2.37 (s, 2H, -CH}_{2}\text{), 3.09 (d, J= 2.7Hz, 1H, -CH), 4.53 (s, 2H, NH}_{2}\text{); \, ^{13}C \, \text{NMR (75 MHz,}
\]
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CDCl3: δ 26.19, 26.31, 26.56, 27.41, 27.84, 29.27, 30.52, 32.05 34.74, 40.67, 43.79, 50.84, 58.91, 114.18, 120.23, 159.87, 163.12, 196.46.

2-amino-4-(4-cyanophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile
(entry 4m, table 2):

Mp. 234-236 °C; IR (KBr): 3423, 3334, 3190, 2918, 2228, 2199, 1679, 1653, 1602, 1498, 1456, 1416, 1332, 762 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ = 2.05 (m, 2H, -CH₂-CH₂-CH₂), 2.37(t, 2H, -CH₂), 2.61 (t, 2H, CO-CH₂), 4.47 (s, 1H), 4.66 (s, 2H, NH₂), 7.37(d, J=8 Hz, 2H, Ar-H), 7.59(d, J=8 Hz, 2H, Ar-H); ¹³C NMR (75 MHz, CDCl₃): δ 20.09, 27.04, 35.73, 36.61, 100, 110, 114.31, 118.41, 119.81, 128.82, 132.64, 148.61, 158, 163.89, 195.84.

2-amino-4-(ferrocenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile
(entry 4n, table 2):

Mp. 200-202 °C; IR (KBr): 3378, 3177, 2959, 2185,1678, 1645, 1602, 1332, 1216, 1030, 808, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 0.96 (s, 3H,CH₃), 1.08 (s, 3H, CH₃), 2.26 (s, 2H, -CH₂), 2.32 (s, 2H, -CH₂), 3.87 (s, 1H, -C₅H₅), 4.02(s, 1H, -C₅H₅), 4.08 (s, 1H, -C₅H₅), 4.22 (s, 5H, -C₅H₅), 4.36 (s,1H, -CH), 4.68 (s, 2H, NH₂); ¹³C NMR (75 MHz, CDCl₃): δ 27.21, 28.45, 29.03, 32.13, 40.61, 50.76, 61.11, 65.73, 66.70, 66.99, 68.09, 69.14, 93.41, 100.00, 160.07, 161.46, 196.18.
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SPECTRAS
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Fig. 14
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